European Journal of Epidemiology **10**: 485–486, 1994.

Influenza vaccines: A main problem in control of pandemics

Youri Ghendon
World Health Organization, Geneva, Switzerland

Abstract. The optimal strategy for control of pandemic influenza is early vaccination with influenza vaccine produced from influenza pandemic strains. However, for pandemic control, vaccine improvements are essential and should include quicker ways of manufacturing and testing of vaccine as well as flexibility on the part of licensing bodies. The production of mass doses of monovalent vaccine in a short time can be more realistic if egg independent production technology can be adopted. In this respect production of an influenza vaccine on a stable cell line can solve many of the problems in increased production of influenza vaccine. But the difficulty with influenza vaccines is that the yield of human influenza viruses on tissue culture is much lower than in embryonated eggs. A new high-yield donor is needed for construction of recombinants with a new pandemic strain, which can replicate in a stable cell line with high titre. The live influenza vaccine may be the most appropriate for prophylaxis of influenza pandemic, as the implementation of this vaccine for mass vaccination is simpler than of inactivated influenza vaccine, and this vaccine, after one immunization of unprime persons, induces local mucocosa immunity which plays an important role in the protection against influenza.

Key words: Influenza, Pandemic, Vaccine

For influenza pandemic control two steps are crucial: first, early detection and isolation of new pandemic variant of influenza virus; second, production of mass doses of monovalent influenza vaccine from a pandemic strain in a very short time.

In the 20th century most of the pandemic strains of influenza virus have originated in the southern part of China [1] and for early detection of new potential pandemic strains a dramatic improvement of influenza surveillance is urgently required in this part of China. With the help of the WHO Collaborating Centre on Influenza in CDC, Atlanta, USA, surveillance of influenza in China has improved significantly in recent years. Most of the new antigenic variants of influenza virus recommended by WHO for vaccine production for the forthcoming epidemiological season have Chinese names. WHO successfully started with collaborating studies in the southern part of China on further improvement of influenza surveillance, studying the mechanism of the origin of pandemic influenza strains in this part of China.

Nevertheless if new pandemic strains of influenza virus are to be detected and isolated very early, the early and mass vaccination with monovalent influenza vaccine produced from influenza pandemic strain, is, perhaps, the only realistic approach for the control of pandemic influenza. However, for pandemic control, vaccine improvements are essential and should include a quicker way of manufacturing and testing the vaccine, and flexibility on the part of licensing bodies.

The experience by the USA in 1976 to control a apparent pandemic of swine influenza shows that the production of influenza vaccine in itself only took 2 months, but the control of the vaccine and the bureaucracy involved took 5 months [2].

It is clear that in the wake of a real influenza pandemic, bureaucratic problems will be solved very quickly – the vaccine can be controlled in parallel by producers and state control authorities – but the main problem remains substrate for vaccine production.

A questionnaire on the possibility of producing mass doses of monovalent influenza vaccine from pandemic influenza vaccine strain in a short amount of time was distributed recently by WHO to 17 main producers of the influenza vaccine. The response was that it is possible, in principle, to produce mass doses of monovalent influenza vaccine in two to three months, but the production of mass doses of vaccine requires a supply of large quantities of embryonated eggs to be planned well in advance.

The production of mass doses of monovalent influenza vaccine in a short amount of time can be more realistic if the egg independent production technology can be adopted. In this respect the production of influenza vaccine on tissue culture can solve any of the problems in the increasing production of influenza vaccine.

The main difficulty in using tissue culture for influenza vaccine production is the low yield of the majority of the human influenza virus strains in this

substrate. In the studies of Tannock et al. [3], it was found that the yield of human influenza virus in primary chicken kidney and chicken embryo kidney cells is only 10^6–10^7 TCD_{50} ml^{-1} and in human diploid cell line it is 100-fold less. Yields of human influenza virus in chicken embryo kidney cells from one embryo grown on roller culture or on the surface of microcarriers are less than those obtained from the allantoic fluids of a whole embryo. But the yield of virus in monolayer cells in Petri dishes is approximately the same as in a chicken embryo. The data shows that, in principle, it is possible to develop conditions for cultivation of human influenza virus in primary tissue culture with the yield no less than in embryonated eggs.

Another possibility is to use stable cell lines for the production of influenza vaccines. It should be noted that WHO has already approved the production of several viral vaccines, including live polio vaccine on stable cell line, and it will be no problem to get this permission for influenza vaccine produced on appropriate stable cell line. The difficulty is that most strains of human influenza virus cannot replicate in stable cell lines at all or the yield of virus is low. A possibility to solve this problem is to select any strain of avian influenza virus (some of them replicate very well in several cell lines), or adapted to stable line strain of human influenza virus. Such avian or human influenza viruses can be used as a master strain for the production of high-yield recombinant for the production of vaccine. However, it can be a problem with the host-range properties of human influenza viruses. It is known that one of the main proteins of human influenza virus, which determines host-range property of this virus is haemagglutinin [4]. If haemagglutinin adapted to stable line high-yield master strain is changed to haemagglutinin of nonadapted new pandemic variants of human influenza viruses it can result in some cases in the inability of the recombinant to replicate in the stable cell line.

Perhaps the best solution to this problem is to use MDCK cell line, in which most of the human influenza viruses replicate well in the presence of trypsin.

If pandemic strains are isolated early and a monovalent inactivated vaccine against a new pandemic strain is produced in 2–3 months, another problem can arise. Due to the limited amount of time to induce an effective immunity against the pandemic strain of influenza virus, the vaccine should be effective after only one injection. However, since most of the population is not primed with the new pandemic strain of influenza virus, the one injection of available inactivated vaccine is incapable of inducing effective immunity to the new strain in the majority of the vaccinees, especially in elderly people. Consequently, to achieve control of the influenza pandemic with inactivated vaccine, a new, strong and safe adjuvant should be developed.

The live influenza vaccine may be the most appropriate for prophylaxis of influenza pandemic, as the implementation of this vaccine for mass vaccination is simpler than that of inactivated influenza vaccine. Live vaccine induces local mucosa immunity which plays an important role in the protection against influenza, and if the vaccine virus is produced on tissue culture, the titre 10^7 TCD_{50} ml^{-1}, such an infectious dose is sufficient to induce an effective immunity. On the other hand there are data that suggest that a live, cold-adapted vaccine can induce an effective immunity in a non-prime person after only one immunization. For example, in the study by Wright & Karzon [5] it was shown that only one immunization with cold-adapted live influenza vaccine H3N2 or H1N1 induced good titre of HA1 antibody in 75–94% of vaccines. At the present time, the many studies with the cold-adapted live vaccine clearly demonstrate immunogenicity and efficacy of this vaccine after one immunization of seronegative persons [5, 6].

As was noted previously, without the production of mass doses of effective influenza vaccine in a short amount of time, the successful control of pandemic influenza is unrealistic. Therefore more attention should be made to serious improvement of the production and efficacy of influenza vaccines.

References

1. Shortridge K. An influenza epicentre? Lancet 1982 (ii): 812.
2. Interagency Work Group on Influenza (HEW, PHS, CDC). Plan for pandemic influenza. Centers for Diseases Control, 8 May 1978.
3. Tannock G, Bryce D, Paul J. Evaluation of chicken kidney and chicken embryo kidney cultures for the large-scale growth of attenuated influenza virus master strain A/Ann/Arbor/6/70-ca. Vaccine 1985; 3: 333–339.
4. Rogers G, Paulson J. Receptor determinants of human and animal influenza virus isolates: Differences in recepter specificity at the H3 hemagglutinin based on species of origin. Virology 1983; 127: 361–173.
5. Wright P, Karzon D. Live attenuated influenza vaccines. Prog Med Virol 1987; 34: 70–77.
6. Ghendon Y. Vaccination against influenza viruses: Current status. Viral Vaccines. New York: Wiley-Liss, 1990: 159–201.

Address for correspondence: Dr Y. Ghendon, World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland
Phone: +41 22 791 2656; Fax: +41 22 788 2937